

Acute interstitial nephritis with Prothionamide

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Abstract

Among drug-related complications, drug-related nephrotoxicity is the commonest. It is the cause for 7% of all drug-related toxicities among inpatients and accounts for 20% to 30% of acute renal failure. Acute interstitial nephritis is one of the drug-related adverse reactions and occurs due to a drug-related type 4 hypersensitivity reaction. In this case report, we reported acute interstitial nephritis that causes acute renal failure (acute kidney injury) in a patient taking Prothionamide therapy. This drug-related side effect had not been reported. In this case report, we report a patient who develops fatigability, rash, and intermittent fever after 14 days of taking the drug Prothionamide. The main aims of this case report are to use it as a pharmacovigilance report for drug-producing companies and to consider a further study on this side effect. It is also an alert for clinicians to consider this side effect when patients develop acute interstitial nephritis while taking Prothionamide.

Keywords

Prothionamide, acute interstitial nephritis, drug-induced acute interstitial nephritis

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Introduction

Among drug-related complications, drug-related nephrotoxicity is the commonest. It is the cause for 7% of all drug-related toxicities among inpatients and accounts for 20% to 30% of acute renal failure.^{1,2} Among drugs mentioned as a cause of drug-induced acute interstitial nephritis (DIN), non-steroidal anti-inflammatory drugs, proton pump inhibitors, angiotensin-converting enzyme inhibitors (ACEIs), and antimicrobials like penicillin are the major ones.³ DIN should be strongly suspected when the typical triad of rash, acute kidney injury (AKI), and eosinophilia occur within a few days of suspected drug commencement. But in some cases, it may happen in <10% of patients within weeks or months after drug commencement.³ Since the commonest etiology of acute interstitial nephritis (AIN) is DIN, which covers 60% to 70% of cases, diagnosing AIN in patients who recently started a new drug is not surprising.^{2,4}

In the more recent drug-resistant tuberculosis (DRTB) treatment guidelines prepared by World Health Organization (WHO), Prothionamide has been given priority due to its high effectiveness and low side effect profile.⁵ When we see Prothionamide efficacy, it has a substantial bactericidal

effect against *Mycobacterium tuberculosis*.⁶ Among the drugs in the ethionamide family, Prothionamide and Ethionamide have similar active ingredients. As a result of this similarity, they can be given interchangeably.⁷ Even if the precise mechanism of action remains unknown, the

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theoretical mechanism is, that after entry to the cell, it will be activated and causes an inhibiting complex that inhibits cellular protein synthesis in the cytosol.⁸ The most known side effects of Prothionamide are nausea and vomiting. The other less common side effects are depression, hallucinations, hypothyroidism, and hyperthyroidism.⁹ Until the day of this case report writing, there were no reported cases of AIN in patients taking Prothionamide.

Case presentation

This drug-related adverse reaction to Prothionamide happened in a 23-year-old patient diagnosed with disseminated DRTB involving the central nervous system (CNS) and lymph nodes and put on a second-line anti-TB (tuberculosis) regimen. He was diagnosed with pulmonary TB a year before and was on anti-TB for 6 months. After treatment completion, his illness was cured. But after 8 months, he began to have headaches, recurrent tonic-clonic seizures, anorexia, fever, and cervical lymphadenopathy. He had a 4 by 3 mm ring-enhancing lesion in the left partial lobe detected from brain magnetic resonance imaging (MRI). Sample taken from the lymph node by fine-needle aspiration cytology (FNAC) was positive for rifampicin-resistant *Mycobacterium tuberculosis*.

Disseminated DRTB involving lymph nodes and brain was diagnosed based on the FNAC and CT (computed tomography) scan results. Then, after a multidisciplinary team discussion, long-term oral regimens (i.e. bedaquiline, levofloxacin, clofazimine, linezolid, and cycloserine) were started. Along with the anti-TB drug, the patient had been on valproic acid for seizure control. The treatment was started while he was at All Africa Leprosy Rehabilitation and Training Center (ALERT) hospital, but the patient was transferred to Mizan-Tepi University Teaching Hospital (MTUTH) after 1 month of treatment follow-up. He had been treated as an inpatient at ALERT hospital and as an outpatient with monthly follow-up after being transferred to MTUTH. In his fourth month of follow-up, he developed QT prolongation (QTc 495 ms) on electrocardiography (ECG) done for routine adverse drug effect monitoring. After checking electrolytes, drug (bedaquiline)-induced QT prolongation was considered, and his treatment regimen was revised by substituting Prothionamide in place of bedaquiline, but the remaining four second-line anti-TB drugs (i.e. levofloxacin, clofazimine, linezolid, and cycloserine).

Prothionamide was discontinued about 14 days after he started taking it following the development of acute renal failure. By reviewing the clinical symptom and laboratory results done from serum and urine samples, AIN secondary to Prothionamide was diagnosed. During this time, renal failure was suspected due to Prothionamide-induced AIN and the multidisciplinary team decided to stop it. But at his fourth visit, that is before Prothionamide was initiated, renal function test, liver function test. Urinalysis and complete blood count were normal except for the ECG, which showed mild QT prolongation. Prothionamide was started at 750 mg/day.

AIN was considered on that day the patient comes to the hospital after he complains of feeling fatigability, rash, and intermittent fever. On examination, he had tachycardia (105 beats per minute) and fever (37.7°C), but the blood pressure was normal (120/70 mm Hg). He had an itchy maculopapular rash around the buttocks and trunk area. From the urine dipstick test done, trace protein-positive results were detected. On urine microscopy, white blood cell count of 15 cells per high-power field (HPF), eosinophil 7 HPF, and 2 red blood cells. Urine cultures taken from the catheter showed no growth. Blood biochemistry showed that erythrocyte sedimentation rate (ESR) was 52 mm/h, C-reactive protein (CRP) was 121 mg/L, creatinine was 2.1 mg/dL, blood urea nitrogen (BUN) was 15 mg/dL, and an estimated glomerular filtration rate (GFR) was 52 mL/min/1.73 m². The biochemistry results which came after day 11 of Prothionamide discontinuation showed that creatinine was 1.1 mg/dL and ESR was 41 mm/h. But after 16 days of Prothionamide discontinuation, renal function, ESR, and urinalysis returned to normal. The RFT (Renal function test) remained to be normal throughout treatment completion. To rule out other causes of AIN, he was asked to take drugs like β -lactams, sulfonamides, macrolides, chloramphenicol, antiviral, nonsteroidal treatment, proton pump inhibitor, H₂-receptor blockers, 5-aminosalicylates, diuretic, but he answered no. He was tested negative for infections that can precipitate AIN like HIV (human immunodeficiency virus), HBV (hepatitis B virus), HCV (hepatitis C virus), and malaria. He was also not taking the herbal medication.

Discussion

Drug-related AIN should be suspected in patients present with elevated urea and creatinine, AIN symptoms, and suggestive urinalysis findings having temporal relation with medication started date.¹⁰ Improvement of symptoms, correction of urinalysis, and blood lab finding after discontinuation of the suspected drug is another strong clue for AIN. Even if the diagnosis confirmed with a renal biopsy, it may not be necessary, especially when there is strong evidence mentioned above.^{1,10} When we saw this patient's case, the patient has elevated urea and creatinine with typical clinical manifestation and laboratory finding that go with AIN, and there was also a close temporal relationship between the start of Prothionamide treatment and the occurrence of AIN. Having this major indicator will strongly suggest the diagnosis of AIN and reduce the necessity of renal biopsy.¹⁰

Virtually all patients diagnosed with AIN will have a rise in the plasma creatinine concentration on presentation, and if the AIN is drug-induced, the increase in creatinine is temporally related to the administration of the suspected drug. The patient was taking other medication before he started on Prothionamide for 4 months, and he does not develop AIN. But the occurrence of AIN after Prothionamide substitution in place of bedaquiline with rapid onset is consistent with a drug-related AIN due to hypersensitivity reaction.^{10,11}

The incidence of major clinical symptom findings reported in two retrospective case series, which collected a total of 121 patients shows rash, fever, eosinophilia, and the triad was observed in 22%, 36%, 35%, and 11%, respectively. As we see patients having triad are only 11 and patients who have all these symptoms are less commonly reported, but if the patient has all these symptoms, it strongly indicates AIN diagnosis.^{11,12} When we see this patient, he has all these mentioned symptoms, which indicate DIN is highly likely.

The other strong indicator following the discontinuation of Prothionamide, the patient's renal function returned to normal while taking other medications in the regimen. In the case of intrarenal ARF Acute re and when we see the renal function test is shown by a BUN-to-creatinine ratio of less than 20, this strongly suggests the intrarenal cause of renal failure.¹²

When we see the above evidence, Prothionamide-induced AIN was the correct diagnosis. Even if a renal biopsy is a perfect method of founding the diagnosis of AIN, unlike in this case it undertook when the diagnosis is uncertain, their contraindications for doing the procedure are not found or a patient does not recover following termination of the assumed medication as the reason of renal failure and AIN. Another disease that may mimic these is drug reactions with eosinophilia and systemic symptoms, which explain the patient's rash and renal condition, but what is against is he has normal liver function and has no eosinophilia.

Conclusion

The major aim of this case report is to highlight pharmacovigilance surveillance reports for drug-producing companies to consider further studies on this side effect. We recommend clinicians consider this side effect when they get AIN in patients who take Prothionamide, which helps in early recognition and treatment. When clinicians consider starting Prothionamide, it is better to do a baseline renal function test. Internists or other physicians and nurses who work in MDR-TB centers should be alert for clinical features that may indicate a probability of DIN that can be corrected, in most cases, by just discontinuing the causative agent.

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Author contributions

Kebede, MA contributes a major part to data collection, organization, and patient care. The other six authors contribute professional comment.

Data availability

The datasets collected and analyzed for the current study are available from the corresponding author and can be obtained upon reasonable request.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics approval

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Informed consent

Written informed consent was obtained from the patient before writing the case report.

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